Individualized treatment of HBsAg-negative chronic hepatitis B using pegylated interferon-alpha2a as first-line and week-12 HBV DNA/HBsAg stopping rule: a cost-effectiveness analysis


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study evaluated the cost-effectiveness of initial treatment with pegylated interferon, with a stopping rule based on hepatitis B virus DNA and hepatitis B surface antigen (HBsAg) at 12 weeks, for patients with hepatitis B e antigen-negative chronic hepatitis B. The authors concluded pegylated interferon, followed by a nucleoside analogue for non-responders, was cost-effective. The clinical evidence was insufficiently discussed, potential comparators were omitted, and the analyses were limited. The validity of the conclusions is unclear.

Type of economic evaluation
Cost-utility analysis

Study objective
This study evaluated the cost-effectiveness of initial treatment with pegylated interferon, with a stopping rule based on hepatitis B virus DNA and hepatitis B surface antigen (HBsAg) at 12 weeks, for patients with hepatitis B e antigen-negative chronic hepatitis B.

Interventions
Eight treatment strategies were compared. Four started with pegylated interferon as the first therapy. After 12 weeks, if a patient had not responded, they either started on the nucleoside analogues tenofovir disoproxil fumarate or entecavir, or they did not start one of these second treatments until cirrhosis developed. The other four strategies had either tenofovir or entecavir as the first therapy, or one of these two treatments after cirrhosis developed.

Location/setting
Italy/secondary care.

Methods
Analytical approach:
A Markov model was developed to model the ongoing risk of disease progression and to calculate the associated costs and utilities. The time horizon was lifetime. The authors stated that the analysis was conducted from the perspective of the Italian National Health Service.

Effectiveness data:
The key clinical data were the probability of not achieving a sustained virological response, and the probability of achieving a virological response and HBsAg clearance after 48 weeks of pegylated interferon. A systematic review was performed to identify the data for the model. Three databases were searched for articles published in English between January 2004 and June 2012. The probability of not achieving a sustained virological response was from a cohort of patients in the PARC trial and a Phase III registration trial. The probability of achieving a virological response and HBsAg clearance after 48 weeks of pegylated interferon, for patients who responded, was from a multicentre, prospective, cohort study. This probability was adjusted assuming all those defined as non-responders did not achieve a virological response.

Monetary benefit and utility valuations:
No quality of life data were identified for Italian patients with chronic hepatitis B. So, the estimates were from a
subgroup of Spanish patients in an international study that used the standard gamble technique.

Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs) gained. QALYs were discounted at 3.5% annually.

Cost data:
The analysis included the costs of drugs, treating different stages of severity of hepatitis B and C, monitoring, and the diagnostic test for identifying a response. Drug costs were those paid by the hospitals, including any discounts. The costs of treating each severity of hepatitis B and C were from a published Italian study that used diagnosis-related group rates and national tariffs. The monitoring costs and the costs of the response test were based on national tariffs. All costs were reported in 2011 Euros (EUR) and inflated where necessary. They were discounted at 3.5% annually.

Analysis of uncertainty:
One-way and probabilistic sensitivity analyses were conducted. The one-way analyses were performed by increasing or decreasing parameter values by 20%. The probability of achieving HBsAg clearance was varied over a set range. The distributions for the probabilistic analysis were defined assuming a standard deviation of 10% of each initial value.

Results
The most QALYs were a result of pegylated interferon then tenofovir before the onset of cirrhosis (15.29 QALYs) and pegylated interferon then entecavir before cirrhosis (15.31 QALYs). The strategies that delayed the nucleoside analogues had poorer outcomes for the patient. Strategies that involved entecavir were consistently more expensive. Pegylated interferon plus tenofovir before cirrhosis cost EUR 59,553 and pegylated interferon plus entecavir before cirrhosis cost EUR 85,228.

Pegylated interferon as a first treatment was dominant compared with the same strategy without pegylated interferon for three strategies, as it was cheaper and more effective. For the fourth strategy, it had an incremental cost-effectiveness ratio (ICER) of EUR 1,152.43 per QALY gained. Early treatment with nucleoside analogues was more expensive and more effective than late treatment, and when comparing the same strategies with early versus late nucleoside analogue treatment, the ICER ranged from EUR 11,796.75 to EUR 20,778.43 per QALY gained.

The likelihood that pegylated interferon plus tenofovir when patients had cirrhosis was cost-effective, compared with no pegylated interferon, at a threshold of EUR 8,000 per QALY gained was nearly 100%.

Authors' conclusions
The authors concluded that initial treatment with pegylated interferon, with a switch to a nucleoside analogue for non-responders, was cost-effective.

CRD commentary
Interventions:
The treatment strategies were described, but it was not clear if all the relevant strategies were included. The authors justified the omission of nucleoside analogues other than tenofovir and entecavir, by stating that these other nucleoside analogues were less clinically effective, but less clinically effective treatments might be more cost-effective and should have been included.

Effectiveness/benefits:
A systematic review of the literature was undertaken to inform the model parameters, which was appropriate, but there was insufficient reporting of the evidence identified, and how specific evidence was selected, to be confident that the best available evidence was used. It was odd that studies in Italian were excluded, as the study was conducted in Italy. Individual studies were chosen for model parameters, rather than using a mixed-treatment meta-analysis to synthesise all the available evidence. A mixed-treatment comparison is generally the most appropriate method for synthesising data on multiple interventions for the same indication. Adverse events were not included. It was stated that fewer than 6% of patients stop treatment due to adverse events, but events that happen to a few patients can significantly affect cost-effectiveness. The efficacy data were from international clinical studies not focused on the population of interest in this study, but the authors showed that these data were generally appropriate.
Costs:
The cost data were from sources relevant to the setting and population. Few details of the costing methods were reported; the source paper was referenced.

Analysis and results:
The authors did not report the aggregate costs and QALYs for all interventions. Pair-wise comparisons were made between pegylated interferon first-line and no pegylated interferon, and between early versus delayed treatment, instead of a full incremental analysis. The cost-effectiveness of pegylated interferon plus tenofovir compared to pegylated interferon plus entecavir was not explored, for example. An analysis comparing all relevant combinations of treatments and treatment timings would have provided better guidance for decision-makers. The probability distributions were not based on empirical data; standard deviations that are 10% of the mean could have underestimated the uncertainty. The probabilistic sensitivity analyses should be treated with caution. The 20% increase or decrease in parameters for the one-way sensitivity analyses might not have covered the relevant range.

Concluding remarks:
There was limited discussion of the clinical evidence used in the model, potential comparators were omitted, and the analyses were limited, making it difficult to assess the validity of the authors' conclusions.

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